



National Prescribing Service Limited

Fact sheet

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## Rosiglitazone and cardiovascular risk

- A recent meta-analysis of clinical trials of rosiglitazone reported that it is responsible for a small but statistically significant increase in the risk of myocardial infarction.
- The meta-analysis has a number of methodological weaknesses.
- No significant increase in the risk of myocardial infarctions has been identified in three large clinical trials of rosiglitazone, yet the result of the meta-analysis remains significant with the inclusion of this data.
- It is still unclear whether rosiglitazone does increase the risk of myocardial infarction. However, the possibility of a small increase in cardiovascular risk should be borne in mind until further evidence becomes available.
- Rosiglitazone is known to increase the risk of heart failure; avoid use in people at an increased risk of heart failure.
- Rosiglitazone should only be used as
  - dual oral therapy in patients with an intolerance or contraindication to metformin or the sulfonylureas
  - triple oral therapy combined with maximally tolerated doses of metformin and a sulfonylurea.
- Insulin can be considered instead of rosiglitazone in these scenarios.

A recent meta-analysis published in the New England Journal of Medicine has raised concerns about a potential increase in risk of myocardial infarction and cardiovascular death among patients treated with rosiglitazone (Avandia).<sup>1</sup>

### What is the evidence for increased cardiovascular risk with rosiglitazone

#### *The meta-analysis*

The meta-analysis aimed to assess the effect of rosiglitazone, in comparison to placebo or an active comparator, on cardiovascular outcomes. It pooled data from 42 studies that randomised patients to rosiglitazone (as monotherapy or as part of a multi-drug regimen) or a regimen that did not contain rosiglitazone. Studies were eligible for inclusion if patients had been exposed to rosiglitazone for at least 24 weeks.

The meta-analysis reported that rosiglitazone was associated with an increased risk of myocardial infarction (odds ratio [OR] 1.43, 95% confidence interval [CI] 1.03 to 1.98,  $p = 0.03$ ).<sup>1</sup> This translates to an increased absolute risk of myocardial infarction among the study population (i.e. the increase that is solely due to rosiglitazone) of less than 1%. The risk of death from cardiovascular causes was also elevated but this did not reach statistical significance (OR 1.64, 95% CI 0.98 to 2.74,  $p = 0.06$ ).<sup>1</sup>

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The absolute event rate was low (approximately 0.6%); there were 86 myocardial infarctions among the 14 736 patients on rosiglitazone and 72 among the 11 635 patients in the comparator group. This may be because most of the studies were of short duration; 23 of the 42 included studies followed patients for six months, and only 12 for one year or more.

The small number of events means that the findings of the meta-analysis could be substantially altered by the misclassification of events. It is possible that events may have been missed or misclassified for the following reasons:

- The authors did not provide detailed information on their search strategy or how they assessed the quality of the studies included in the meta-analysis.
- Six otherwise eligible studies were excluded from the meta-analysis because they did not provide information on myocardial infarctions or cardiovascular death.
- The meta-analysis relied on summary information from the manufacturer's (GlaxoSmithKline) clinical trial register or FDA briefing documents for 29 of the 42 studies because the results had not been published publicly.
- The definition of what constituted a myocardial infarction or a cardiovascular death differed between the individual studies included in the meta-analysis.

In addition, information about the baseline cardiovascular risk of patients included in the original studies was lacking and the authors of the meta-analysis did not perform any sensitivity analyses to explore whether altering assumptions made in the meta-analysis had an impact upon its findings.

The above makes it difficult to assess whether the meta-analysis findings are reliable. However, an independent meta-analysis conducted by GlaxoSmithKline and submitted to the FDA also found a significant increase in the risk of myocardial infarction (hazard ratio [HR] 1.31, 95% CI 1.01 to 1.70).<sup>2</sup> The fact that many of the studies included in both meta-analyses had relatively short durations of follow-up raises the possibility that the increased rate of myocardial infarction could become more evident with longer term use.

### ***Large clinical trials***

Three large randomised controlled trials (n>4000 per trial) of rosiglitazone have published final or interim results. Two of these trials — Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) and A Diabetes Outcome Progression Trial (ADOPT) — were included in the meta-analysis. The RECORD trial (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes) released interim results shortly after the meta-analysis was published.

### ***The RECORD trial was not included in the original meta-analysis***

Following the controversy ignited by the meta-analysis, an interim safety analysis of the RECORD trial was published.<sup>3</sup> RECORD compares the outcomes of patients on rosiglitazone and metformin/sulfonylurea to those among patients on metformin and a sulfonylurea. Patients with cardiovascular disease (including heart failure) were excluded from the trial.

The interim analysis showed a small increase in the number of myocardial infarctions and a small decrease in the number of cardiovascular deaths but these differences were not statistically significant. As a result the trial's data and safety monitoring committee has recommended that it continue for another two years as originally planned.<sup>3</sup>

Adding these interim results to the meta-analysis did not change its findings.<sup>4</sup> Rosiglitazone remained associated with an increased risk of myocardial infarction (OR 1.33, 95% CI 1.02 to 1.72,  $p =$  not reported). Amended estimates of risk of cardiovascular death were not provided.

### *Trials included in the meta-analysis*

ADOPT and the DREAM trial were the two largest trials included in the meta-analysis. DREAM randomised patients with pre-diabetes to placebo or rosiglitazone.<sup>5</sup> ADOPT randomised patients with recently diagnosed type 2 diabetes who had not been treated with a pharmacotherapy to rosiglitazone, metformin or a sulfonylurea (glibenclamide).<sup>6</sup> Patients with a history of cardiovascular disease (including heart failure) were excluded from both studies.

Both studies reported a small but statistically insignificant increase in the number of myocardial infarctions among patients treated with rosiglitazone.<sup>5-7</sup> Both trials reported significantly higher rates of heart failure, oedema and weight gain among the rosiglitazone patients.<sup>5-7</sup>

### **Summary of the evidence**

The individual trials do not report a significantly greater risk of myocardial infarction or cardiovascular death among patients on rosiglitazone (Table 1). In contrast, the meta-analysis reported that the myocardial infarction rate was significantly higher among those on rosiglitazone (Table 1).

A meta-analysis increases the power available to observe the effect of a treatment by increasing the total study population and number of events. However it is important that the studies pooled are sufficiently similar, and that all studies of relevance are included, to avoid the risk of bias.

There are methodological problems with the meta-analysis which cast reasonable doubt upon the clinical significance of the results it reports. Even so, the possibility of a small increase in cardiovascular risk should be borne in mind until further evidence becomes available. Prescribers should take particular care when prescribing the drug to patients with a high risk of cardiovascular disease.

**Table 1: Summary of the meta-analysis and the large prospective clinical trials**

Source	N	Study population	Relative risk* of MI (95% CI)	Proportion experiencing MI	Relative risk* of CV death (95% CI)	Proportion experiencing CV death
Meta-analysis <sup>1</sup> vs placebo or non-rosiglitazone regimen	27 847	Any patient included in one of the eligible studies – includes patients with type 2 diabetes, pre-diabetes, Alzheimer's, and psoriasis	OR 1.43 (1.03 to 1.98) <sup>†</sup>	Control: 0.62% Rosiglitazone: 0.60%	OR 1.64 (0.98 to 2.74)	Control: 0.23% Rosiglitazone: 0.36%
Meta-analysis including RECORD data <sup>4</sup>	32 294	See above	OR 1.33 (1.02 to 1.72) <sup>†</sup>	—	not reported	—
RECORD <sup>3</sup> vs metformin & sulfonylurea	4 447	Type 2 diabetics with no cardiovascular disease	HR 1.16 (0.75 to 1.81)	Control: 1.7% Rosiglitazone: 1.9%	HR 0.83 (0.51 to 1.36)	Control: 1.6% Rosiglitazone: 1.3%
DREAM <sup>5</sup> vs placebo	5 269	Pre-diabetics with no cardiovascular disease	HR 1.66 (0.73 to 3.80)	Control: 0.3% Rosiglitazone: 0.6%	HR 1.20 (0.52 to 2.77)	Control: 0.4% Rosiglitazone: 0.5%
ADOPT <sup>7</sup> vs metformin	4 351	Recently diagnosed type 2 diabetics with no cardiovascular disease	HR 1.23 (0.68 to 2.22)	Control: 1.4% Rosiglitazone: 1.6%	HR 1.30 (0.35 to 4.86)	Control: 0.3% Rosiglitazone: 0.3%
vs glibenclamide			HR 1.52 (0.79 to 2.94)	Control: 1.0% Rosiglitazone: 1.6%	HR 0.58 (0.19 to 1.78)	Control: 0.6% Rosiglitazone: 0.3%

CI – confidence interval, CV – cardiovascular, HR – hazard ratio, MI – myocardial infarction, OR – odds ratio

\* The risk of an event in the treatment group compared to the risk of that event in the control group. An OR (or HR) of 1.43 means that the risk of an MI is 43% higher among patients on rosiglitazone than in patients not on rosiglitazone.

† Significant result.

## What does this mean for people with type 2 diabetes?

Glitazones (rosiglitazone or pioglitazone) cause weight gain, oedema and increase the risk of heart failure.<sup>8</sup> They should not be used in patients with New York Heart Association (NYHA) class III or IV heart failure. Health professionals should also take care when prescribing glitazones to women given recent reports of an increased risk of fractures among this group.<sup>9,10</sup>

### ***Patients not currently taking rosiglitazone***

Rosiglitazone is a third-line choice therapy and is not PBS listed as a monotherapy. It should not be the first-choice drug for newly diagnosed patients with uncontrolled blood glucose levels. A recent Cochrane review has suggested that clinicians use other anti-diabetic medications where possible given a lack of evidence that rosiglitazone improves diabetes-related morbidity and mortality compared with other oral anti-diabetics.<sup>11</sup>

Metformin is the first-line choice for patients with type 2 diabetes.<sup>12</sup> It improves glycaemic control and lower all-cause mortality, myocardial infarction, diabetes-related complications and diabetes-related death.<sup>13</sup> A sulfonylurea should be used for patients in whom metformin is contraindicated.

If glycaemic control is no longer achievable by metformin (or a sulfonylurea) alone, a combination of metformin and a sulfonylurea is the preferred approach. A glitazone should only be considered when a combination of metformin and a sulfonylurea fails to maintain glycaemic control or when a

patient has an intolerance or contraindication to one of these drugs. Insulin may be a better option than a glitazone in these situations.<sup>12</sup>

### **Options for patients already taking rosiglitazone**

Rosiglitazone is only PBS-listed for:

- dual oral therapy when patients have an intolerance or contraindication to metformin or a sulfonylurea
- triple oral therapy combined with maximally tolerated doses of metformin and a sulfonylurea.

It is too early to recommend that patients on rosiglitazone cease this medication given the uncertainty around any increase in the risk of myocardial infarction or cardiovascular death. It is also unclear whether any potential increase in cardiovascular events outweighs any improved glycaemic control that rosiglitazone may offer.

Prescribers may wish to consider replacing rosiglitazone with insulin. Insulin is known to reduce the risk of diabetic complications<sup>14</sup> and has a better established safety profile than rosiglitazone. Start with 10 Units of isophane insulin at bedtime while continuing metformin, a sulfonylurea or both.<sup>8</sup> For more details, see *NPS News 39: Reducing risk in type 2 diabetes* (<http://www.nps.org.au/healthpro>, then choose Newsletter Index in the left-hand panel).

### **Pioglitazone**

There is insufficient evidence to draw conclusions about pioglitazone (Actos) and the risk of cardiovascular death or myocardial infarction. One large trial which randomised patients with type 2 diabetes and a history of cardiovascular disease (excluding heart failure) to pioglitazone or placebo reported a significant improvement in a secondary end-point of all-cause mortality, myocardial infarction and stroke.<sup>15</sup> It is unclear whether pioglitazone would improve these outcomes among patients with type 2 diabetes and no history of cardiovascular disease.

Pioglitazone is not PBS listed for use as a monotherapy or as a triple oral therapy.

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The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decision based on this information should be made in the context of the clinical circumstances of each patient.